CHRONIC TOXICITY SUMMARY

ETHYL CHLORIDE

(Chloroethane; monochloroethane; ether hydrochloric)

CAS Registry Number: 75-00-3

I. Chronic Toxicity Summary

Inhalation reference exposure level	**30,000 µg/m^3** (10,000 ppb)
Critical effect(s)	Delayed fetal ossification in mice
Hazard index target(s)	Teratogenicity; alimentary system

II. Physical and Chemical Properties (HSDB, 1995; 1999)

Description	Colorless gas
Molecular formula	C_2H_5Cl
Molecular weight	64.52
Density	0.9214 g/cm^3 @ 0°C
Boiling point	12.3 °C
Melting point	–138.7 °C
Vapor pressure	1000 torr @ 20 °C
Conversion factor	1 ppm = 2.64 mg/m^3 @ 25°C

III. Major Uses or Sources

Ethyl chloride has been used as a starting point in the production of tetraethyl lead and as a refrigerant, solvent and alkylating agent (HSDB, 1995). It is also used as a topical anesthetic (Clayton and Clayton, 1994). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 291,300 pounds of ethyl chloride (CARB, 1999).

IV. Effects of Human Exposure

Neurological symptoms have been observed in human case studies in instances of ethyl chloride abuse. Cerebellar-related symptoms including ataxia, tremors, speech difficulties, and hallucinations were observed in a 28-year old female who had sniffed 200-300 ml ethyl chloride off her sleeve daily for 4 months (Hes *et al.* 1979). The patient's liver was enlarged and tender. Four weeks following cessation of exposure, all symptoms were absent.

V. Effects of Animal Exposure

Pregnant mice were exposed to 1300, 4000, or 13000 mg/m^3 ethyl chloride in air for 6 hours per day on days 6-15 of gestation (Scortichini *et al.*, 1986). No effects on fetal resorption rates, litter size, body weight or maternal health were observed. A statistically significant increase in the incidence of delayed ossification of the skull bones was observed in fetuses from the 13,000 mg/m^3 (4900 ppm) ethyl chloride exposed group. This skull effect was accompanied by a non-significant increased incidence of cervical ribs (a supernumerary rib is considered to be a malformation). No significant adverse effects were observed in fetuses from the 4000 mg/m^3 (1500 ppm) exposure group.

No significant adverse effects were observed in rats and mice exposed to 0 or 15,000 ppm ethyl chloride for 6 hours per day, 5 days per week for 102 weeks (rats) or 100 weeks (mice) (NTP, 1989). At necropsy, a complete histopathologic examination (approximately 35 tissues) failed to identify evidence of non-cancer toxicity. The same study also exposed rats and mice to 2500, 5000, 10,000 or 19,000 ppm ethyl chloride 6 hours per day, 5 days per week for 13 weeks. No exposure-related clinical signs of toxicity or histological changes were observed in exposed animals. Thus the subchronic NOAEL for mice and rats is 19,000 ppm, which is equivalent to a continuous exposure of 3400 ppm, and a free-standing chronic NOAEL is 15,000 ppm, which is equivalent to a continuous exposure of 2700 ppm (7100 mg/m^3).

Increased relative liver weights and a slight increase in hepatocellular vacuolation were observed in mice exposed to 5000 ppm ethyl chloride 23 hours per day for 11 days (Landry *et al.*, 1989). No effects were observed in mice exposed to 0, 250, or 1250 ppm ethyl chloride for the same period.

Following acclimatization to an inhalation chamber, two groups of 10 female mice were exposed to 0 or 15,000 ppm (40,000 mg/m^3) ethyl chloride 6 hours per day for 2 weeks (Breslin *et al.*, 1988). Groups of five male mice were housed in each inhalation chamber to synchronize and promote regular cyclicity. The mean length of the estrous cycle in control mice remained constant at 4.5 days during both pre-exposure and exposure periods. Mice in the 15,000 ppm exposure group showed a 0.6 day increase in the mean cycle length during exposure (5.6 days) when compared to the pre-exposure period (5.0 days). The authors attribute this increase in estrous cycle length to a general stress response although they note that it does not preclude direct effects on neuroendocrine function.

VI. Derivation of Reference Exposure Level

Study	Scortichini *et al.*, 1986
Study population	Mice
Exposure method	Discontinuous whole-body inhalation (on days 6-15 of gestation)
Critical effects	Delayed ossification of skull foramina
LOAEL	13,000 mg/m^3
NOAEL	4,000 mg/m^3
Exposure continuity	6 hours per day
Exposure duration	Days 6-15 of gestation
Average experimental exposure	1,000 mg/m^3 for NOAEL group (4000 x 6/24)
Human equivalent concentration	1,000 mg/m^3 for NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	30 mg/m^3 (30,000 µg/m^3; 10 ppm; 10,000 ppb)

To develop the chronic REL OEHHA used the same study on which U.S. EPA based its RfC of 10,000 µg/m^3. The REL is based on a developmental toxicity study. In accordance with U.S. EPA methodology, a time-weighted average concentration for the discontinuous exposure experiment is not used by U.S. EPA when the key effect is developmental toxicity. However, OEHHA prefers to make a time adjustment to equivalent continuous exposure because the chronic REL assumes continuous exposure. U.S. EPA also used a Modifying Factor (MF). The database deficiencies leading U.S. EPA to employ a modifying factor include the lack of a multigenerational reproductive study. The criteria for use of such modifying factors are not well described. Such MFs were not used by OEHHA.

As a comparison to the proposed REL of 10 ppm, NTP (1989) found a free-standing NOAEL of 15,000 ppm in rats and mice exposed to ethyl chloride for 6 hours per day, 5 days per week for 2 years. Time adjusting to continuous exposure results in an adjusted NOAEL of 2679 ppm. Applying an RGDR of 1, a UF_A of 3 and a UF_H of 10 results in an estimated REL of 90 ppm.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for ethyl chloride include the availability of controlled exposure inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathogical analysis, and the observation of a NOAEL. Major areas of uncertainty are the lack of adequate human exposure data, and the lack of a multigenerational reproductive study.

VIII. References

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